# Computational Modeling of Optogenetic Control of Neuronal Signaling

*A synopsis of the proposed thesis to be submitted for the degree of*

**DOCTOR OF PHILOSOPHY**

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# 1. INTRODUCTION

Optogenetics is a revolutionary technique, combining genetics and optics to achieve gain or loss of functions of well defined events within specific cells of living tissue. This technique, especially allows targeted, fast control of neuronal activities in biological systems as complex as freely moving mammals, with unprecedented temporal and cell specific spatial resolution (Deisseroth *et al.,* 2006). In contrast, electrical stimulation commonly used to study neural circuits lacks in specificity.

Since its introduction in 2005, optogenetics has found widespread applications, initially in neuroscience (Zhang *et al.*, 2006; Adamantidis *et al.*, 2007; Arenkiel *et al*., 2007; Han and Boyden, 2007; Yizhar *et al.*, 2011), but increasingly also in more distal areas of physiology such as cardiology (Arrenberg *et al.*, 2010; Boyle *et al.*, 2013), intracellular signaling (Airan *et al.*, 2009), and gene transcription (Konermann *et al.*, 2013). Applications to date includes control of motor cortex (Aravanis *et al.*, 2007), cortical circuit mapping (Wang *et al.*, 2007; Zhang *et al.*, 2007; Ayling *et al.*, 2009; Petreanu *et al.*, 2009; Klapoetke *et al.*, 2014), optoelectronic neuroprosthetic devices such as retinal or cochlear prostheses (Lagali *et al.*, 2008; Degenaar *et al.*, 2009; Busskamp & Roska, 2011, Hernandez *et al.*, 2014), regulation of the symptoms of neurodegenerative disorders of Parkinson's (Gradinaru *et al.*, 2009), closed loop control of epileptic seizures, peripheral nerve stimulation (Arlow *et al.*, 2013), and novel cardiac pacemaker technology (Bruegmann & Sasse, 2015), to name just a few (Evans *et al.,* 2016). On the basis of its fast growing applications in many fields of biomedical research, *Nature Methods* selected optogenetics as ‘Method of the Year’ in 2010 (Deisseroth, 2011).

The information between neurons is encoded into sequence of identical spikes or action potential, which appear in spatial and irregular temporal patterns. These spikes directly influence the motor action of freely moving mammals (Ignatov *et al.,* 2015). In order to control the behavior of the mammals, it is desirable to find a way to modulate these spike trains with high temporal and spatial resolution. Optogenetics facilitates the excitation, inhibition or modulation of these spike trains with light at millisecond temporal and cell specific resolution (Deisseroth *et al.,* 2006). In optogenetics, neurons are first genetically engineered to express light-sensitive proteins (opsins). When these neurons are then illuminated with light of the correct frequency, the spikes or action potential can be activated or inhibited, depending on the particular kind of opsin that was chosen for expression (Guru *et al.,* 2015).

In optogenetics, diverse light-sensitive proteins from eyes, plants, fungi, jellyfish, coral, bacteria and algae have allowed versatile control over neuronal activity using wide range of light spectrum (Repina *et al.,* 2017). Microbial rhodopsin pumps and channels are

most prominent and widely used opsins for optogenetic switching of neurons (Govorunova *et al.,* 2017a). The first of these neuronal switches used Channelrhodopsin-2 (ChR2), when expressed in neurons and exposed to blue light, this nonselective cation channel immediately depolarizes the neuron and triggers a spike (Boyden *et al.,* 2005). As demonstrated by the pioneering experiment, very short (millisecond) pulses of light can be used to induce single action potentials in ChR2-expressing neurons, and spiking activity can be controlled at frequencies approaching 30 spikes per second (Guru *et al.,* 2015). This initial demonstration of ChR2 was soon followed by a number of reports confirming its function in neurons (Li *et al.,* 2005; Ishizuka *et al.,* 2006).

After successful application of ChR2, it was engineered to optimize expression and photocurrent in mammalian systems (Nagel *et al.,* 2005; Gradinaru *et al.,* 2007). Through these efforts, opsins having extremely fast kinetics, named ChETA, CatCh and ChEF/ChIEF were evolved (Lin et al., 2009; Gunaydin et al., 2010; Mattis et al., 2012). These tools provide extremely fast temporal control over neuronal activity. In addition, these opsins reduce the occurrence of doublet or triplet spikes resulting from a single light pulse, sometimes problematic when using ChR2, if the expression level is not tightly controlled.

To modify the spontaneous firing rate of neural population rather than control of spike generation, step-function or bi-stable opsins such as ChR2 (C128A), ChR2 (C128T) and ChR2 (D156A) as useful tools were created by modifying ChR2. These opsins stabilize the open conducting state for a longer time (Berndt *et al.,* 2009, Bamann *et al.,* 2010). When using these opsins, photocurrent can be initiated with a brief blue light pulse and terminated with a yellow light pulse. Another advantage is high-sensitivity to light of these opsins, which makes them useful for their use in neuron with a light source several millimeters away (Tye & Deisseroth, 2012).

Various red-shifted opsins have also been engineered, due to red light capability to penetrate deeper in tissue, as another effort to find a noninvasive way of treatment. The first red-shifted opsin VChR1, having significant shifted peak ~ 535 nm, when compared to ChR2 at 460 nm were engineered (Zhang *et al.,* 2008). However, low photocurrent generation in mammalian system hide the utilization of VChR1. Another variant C1V1 also exhibits red-shifted peak absorption, but has slow kinetics compared to ChR2. Consequently, ReaChR (peak response at 590-630 nm) has shown enhanced membrane trafficking and expression in mammalian cells with faster kinetics and higher photocurrent (Lin *et al.,* 2013). More efforts led to a newly-discovered pair of opsins, named Chronos (a blue and green light-sensitive opsin with high light sensitivity and fast kinetics) and Chrimson (an opsin with an excitation spectrum 45 nm red-shifted from previous ChRs). The combination of these opsins offers two-color activation of neuronal spiking in independent neuronal populations without detectable crosstalk (Klapoetke *et al.,* 2014).

It is desirable to inhibit neuronal signaling instead of triggering it. Light stimulation of halorhodopsin (NpHR), a chloride pump, hyperpolarizes neurons and inhibit spikes in response to yellow light (Han & Boyden, 2007; Zhang *et al.,* 2007). NpHR pumps chloride ions into the cell upon light activation, resulting in inhibition of action potential. A new opsin eNpHR3.0, engineered from NpHR, has improved surface membrane localization and a large photocurrent (Gradinaru *et al.,* 2008, 2010; Zhao *et al.,* 2008). eNpHR3.0 can be driven by green, yellow, or red wavelengths of light, with an excitation maximum at 590 nm, enabling the use of less expensive laser systems. For the treatment of neurological disorders such as epilepsy in animal models, inhibitory proteins have provided efficient results (Tonnesen *et al.,* 2017; Guru *et al.,* 2015).

To inhibit neurons through hyperpolarization, proton pumps can also be used, which pump protons out of the cell, and have some features that make them desirable alternatives to chloride pumps, which include fast recovery from inactivation and high light-driven currents. Arch (archaerhodopsin-3 from *Halorubrum sodomense*), Mac (from the fungus *Leptosphaeria maculans*), ArchT (an archaerhodopsin from *Halorubrum* strain TP009), and eBR (an enhanced version of bactereorhodpsin from *Halobacterium salinarum*) are proton pumps that show robust efficiency in inhibition (Chow et al., 2010; Gradinaru et al., 2010; Han et al., 2011). Initial inhibitory variants, like NpHR, were plagued by issues with cellular localization and toxicity, but new versions have eliminated or greatly reduced these problems (Mattis et al., 2012).

More recently, spectrally-shifted inhibitory opsins have also been developed. The chloride and proton pump inhibitory opsins, discussed above, are significantly red-shifted from ChR2. Development has focused on finding or developing even more red-shifted inhibitory opsins, for maximal and potentially non-invasive light penetration into the brain. Recently, Chuong et al., (2014) discovered and optimized a red-shifted cruxhalorhodopsin, named Jaws, which is a chloride pump from *Haloarcula salinarum*. Jaws is a highly light-sensitive opsin with photocurrents three times as large as those of other known inhibitory opsin. This molecular tool is particularly useful for noninvasive neuronal inhibition in deep brain structures, or more effective inhibition in larger primate brains. Two excellent recent studies used the crystal structure of channelrhodopsin hybrid C1C2, determined by Kato et al. (2012), to create a class of light-activated inhibitory chloride channels (Berndt et al., 2014; Wietek et al., 2014). iC1C2 allows for blue-shifted inhibition with fast kinetics, while SwiChR provides step function inhibition. The latest version of the fast mutants, iC++, permits inhibition of evoked neuronal spiking at higher injected currents than the chloride pump eNpHR3.0 (Berndt *et al.,* 2016; Wietek *et al.*, 2015).

Recently, new screening efforts have unveiled a new class of natural anion channelrhodopsins (nACRs) from different cryptophyte species that provide highly sensitive

and efficient hyperpolarization and neuronal silencing through selective anion conduction (Govorunova *et al.,* 2015). The nACRs derived from *Guillardia theta,* named GtACR1 & GtACR2, have shown complete inhibition of cardiomyocyte electrical activity under conditions in which Arch was inefficient (Govorunova *et al.,* 2016). Malyshev *et al.* have found that despite strong inhibition of light stimulation of GtACR2 expressing neurons can surprisingly lead to generation of action potentials, presumably initiated in the axonal terminals (Malyshev *et al.,* 2017). Consequently, Mohammad *et al.,* have shown that *Gt*ACR1 & *Gt*ACR2 can be used to specifically and rapidly inhibit neural system involved in *Drosophila* locomotion, wing expansion, memory retrieval and gustation, thus demonstrated their broad utility in the circuit analysis of behavior (Mohammad *et al.,* 2017). Another notable variant named ZipACR showed a large variation of the amplitude, kinetics (current half-decay time 2-4 ms), and spectral sensitivity of its photocurrents. ZipACR expressed in cultured mouse hippocampal neurons enables precise photoinhibition of individual spikes in trains of up to 50 Hz (Govorunova *et al.,* 2017b).

To better understand the contribution of specific cell types to the physiology of neuropsychiatric disease, a pair of microbial light-sensitive proteins both for inhibition and excitation, when used together, can optically interrogate intact neural circuits and bidirectionally control animal behavior (Zhang *et al.,* 2007). Han and Boyden have shown that trains of yellow and blue light pulses can drive high-fidelity sequence of hyperpolarizations and depolarizations in neurons simultaneously expressing yellow light-driven halorhodopsin (NpHR) and blue light-driven ChR2 (Han & Boyden, 2007).

Due to high absorption and scattering coefficients, visible light, cannot reach the inner depths of the brain. Two-photon excitation technique uses infra-red light sources and provides a better spatial specificity and deeper penetration in scattering tissue. Two-photon optogenetic activation of neurons, originally demonstrated with ChR2 (Rickgauer & Tank, 2009). Consequently, it has also been observed with red-light activated C1V1 (a ChR variant from *Volvox carteri*) variants (Packer et al., 2012, 2015; Prakash et al., 2012; Rickgauer et al., 2014). Two groups Rickgauer *et al.,* (2014) and Packer et al., (2015) combined two-photon population calcium-imaging with two-photon optogenetics, to achieve simultaneous readout and manipulation with single-cell. Chaigneau *et al.* have demonstrated reliable action potential generation in ReaChR-expressing neurons and studied holographic two-photon evoked spiking performances depending on illumination power and pulse-width (Chaigneau *et al.,* 2015). Recently, two-photon holographic photoactivation of Chronos has also shown neuronal firing with sub-millisecond optogenetic control (Ronzitti *et al.,* 2016). The exciting area of optogenetics has primarily been driven by path breaking experimental studies. However, the need to understand the photodynamics also requires rigorous theoretical studies through computational optogenetics.

## 1.1. Computational Optogenetics

Computational optogenetics has opened up tremendous opportunity to understand optogenetics and explore its applications through theoretical studies. It helps to simulate photostimulation of protein expressing neurons (Wong *et al.,* 2012). To treat any psychiatric disorder using optogenetics, it is required to formulate a pre-protocol of the treatment. For such cases, computational optogenetics provides the predefined and highly precise data-set of parameters such as intensity, wavelength, pulse-width, concentration etc. It can aid in quick (virtual) testing of the behavior of newly developed light sensitive proteins in a wide range of cell types and within realistic tissue settings. Also, theoretical simulation assists in the proper interpretation of experiments within a complex cell/tissue environment, which is often questionable and challenging (Williams *et al.,* 2013). The development of new optogenetic proteins that allow for more efficient photo-stimulation can be guided by computational prediction of the response of different cells and tissues to light. Due to the naturally occurring structural diversities in living animals and tissues, a huge amount of data-set is required for optogenetics to be used in different circumstances, which is a challenging task. In that case, computational optogenetics assists in providing pre-defined values of parameters to be used for different experimental environments.

Computational optogenetics aims to formulate accurate mathematical models of light-controlled opsin-expressing neuronal firing. To achieve this objective, the following is required;

1. To accurately model the photoresponse of light-sensitive proteins, and
2. To integrate the above model with an accurate neuron model to analyze protein expressing neuronal signaling.

From the modeling perspective of light-sensitive proteins used in optogenetics, two transition rate models, a 3-state and a 4-state model are currently available to mimic their photocurrents, which are in good agreement with experimental measurements (Nikolic *et al.* 2006, 2009). Nikolic *et al.* conducted electrophysiological studies of the photokinetics of hippocampal cells expressing ChR2, for various light stimulations and showed the limitations of the previously suggested 3-state model and identify a four-state model that accurately follows the bi-exponential decay in photocurrent of ChR2 (Nikolic *et al.,* 2009). Consequently, to understand the dynamics of the ChR2-evoked spikes subject to various stimulation protocols, Grossman *et al.* developed a model that describes the response of ChR2-expressing neurons to light stimuli and used that model to explore the light-to-spike process. They concluded that an optimized stimulation is achieved when the optical energies are delivered in short pulses (Grossman *et al.,* 2011). However ChR2 can drive spiking with millisecond precision in a wide variety of cells, tissues and animal species, although several

properties of this protein limit the precision of optogenetic control. As mentioned earlier, to overcome these limitations, the effect of mutation was explored to create new variants. Two new ChR2 variants, namely, ChETA and ChRET/TC were engineered (Gunaydin *et al.,* 2010; Berndt *et al.,* 2011). In order to determine which of the models can effectively capture the dynamical response of the neurons expressing these variants, Stefanescu *et al.* incorporated these models into various neuron models and concluded that the 4-state model was able to capture neural response consistent with experiments across a wide range of optostimulation protocols (Stefanescu *et al.*, 2013). Grossman *et al.,* have investigated how the spatial pattern of excitation affects the response of ChR2 expressing neurons via simulation (Grossman *et al.,* 2013).

The application of cardiac optogenetics is also emerging as an exciting new potential avenue to enable spatiotemporal control of excitable cells and tissues in the heart with low-power optical stimuli. Recently, a multi-scale computational tool named PyRhO has also been developed to characterize new (and existing) opsins by automatically fitting a minimal set of experimental data to three, four, or six-state kinetic models and to simulate these models at the channel, neuron and network levels (Evans *et al.,* 2016).

Although, accurate modeling of photoresponse of ChR2, ChETA and NpHR, and light-controlled neuronal signaling of neuron expressing them have been reported. Some more potent and useful opsins that have been recently discovered have not been theoretically studied.

## 1.2. Challenges

The new and very fast growing field of ‘Optogenetics’ was established to understand the working of the brain and to find the cause and cures for neurological diseases such as, Parkinson’s, Alzheimer, Epilepsy, Depression and malfunctions in vision. Although it has been used to study different mammals, the ultimate challenge is to undertake human trials. Of course, without human trials it is impossible to know whether microbial gene products will be well tolerated in the human body (Boyden, 2015). Another challenge is to understand the information transfer and processing within the mammalian nervous system (Chen *et al.,* 2017), to understand the working of human brain.

In order to face the challenges, a large number of light-sensitive proteins have been developed to perform the desired action. Some of the photoreceptors provide fast kinetics which allow to switch on or off the neurons with millisecond precision. These fast proteins provide a good platform to understand the information processing between neurons. Most of present optogenetic proteins utilize visible light which limits their application for deeper tissue stimulation. New tools, sensitive in the longer range of the electromagnetic spectrum (e.g.,

infrared or radio frequency), are desirable since they would allow deeper tissue penetration and perhaps even facilitate non-invasive approaches. With increasing knowledge of the mechanisms of action of these proteins and the complexities of their application in neural systems, new tools need to be engineered such that they maximally fulfill their intended function and allow predictable, well-controlled manipulation of neural activity (Pashaie *et. al.* (2014)).

In an effort to develop more effective and tailored opsins, hybrids and genetic mutants are continually being created (Berndt et al., 2008; Lin et al., 2009; Hegemann & Moglich, 2011; AzimiHashemi et al., 2014). Experimentally characterizing these new variants is a lengthy process requiring substantial effort before they can be harnessed to address questions in neuroscience (Chow *et al*., 2010; Gunaydin *et al.*, 2010; Lin, 2011; Chuong *et al.*, 2014). The problem is further compounded when considering the number of combinations between opsins (with total variations now in the hundreds, Zhang *et al.,* 2011) and target cell types. Experimentally testing each combination of opsin and target cell type of interest is not practically feasible, effectively limiting the use of optogenetics as a tool (Evans *et al.,* 2016).

Hence, computational optogenetics is a better platform to resolve the above limitations. It can guide to engineer such proteins which would allow well-controlled neuronal manipulation. Only a few theoretical models have reported so far, which highlights the urgent need to develop accurate computational models of newly discovered light-sensitive proteins integrated neurons and verify the reported experimental results.

## 2. MOTIVATION

Computational optogenetics has tremendous scope of research. It assists in the proper interpretation of experiments within a complex cell/tissue environment, which is often ambiguous and challenging. The available theoretical models of optogenetic photoreceptors enhanced their applicability over a wide range of cell types. Theoretical models have been reported to mimic the photocurrent of ChR2, ChETA and NpHR proteins only. Theoretical models to mimic the photoresponse of a number of newly discovered light-sensitive proteins, with better control of neuronal signaling, have not been investigated. Hence, we have been motivated to develop accurate theoretical models of optogenetic control of these recently discovered proteins expressed neurons. Further this detailed study would also help in optimization of neuronal signaling, by finding optimum values of various physical parameters, which would be useful for both understanding the reported experiments, and design better experiments and neuromorphic devices.

# 3. OBJECTIVES

The objective of the proposed thesis is to undertake a detailed theoretical study by developing accurate theoretical models to achieve fast, non-invasive and bi-directional control over neuronal signaling.

For optogenetics, identifying variants with well separated absorption spectra is of great interest, for multiplexed control of excitation and inhibition by different colors of light in a single cell or in a population of cells. Lin *et al.,* reported Red-activatable Channelrhodopsin (ReaChR) that is optimally excited by orange-red light with wavelength ~ 590- 630 nm (Lin *et al.,* 2013).

In an effort to develop more effective and tailored inhibitory opsins, hybrids and genetic mutants are continually being created. Recently, a new red-shifted cruxhalorhodopsin, Jaws, derived from *Haloarcula Salinarum* has shown non-invasive optical inhibition of neurons deep in the brain of awake mice (Chuong *et al.,* 2014). Another advantage is that, Jaws has much faster kinetics ($t_{off}$ ~ 7 ms) and much higher photocurrent, three times as large as those of previously reported inhibitory opsins (Guru *et al.,* 2015).

In parallel, new screening efforts have unveiled a new class of natural anion channelrhodopsins (nACRs) from cryptophyte alga *Guillardia theta* (Govorunova *et al.,* 2015). These rhodopsin channels, named GtACR1 and GtACR2, have near-perfect anion selectivity and produce several fold larger photocurrents in mammalian cells than any previously discussed engineered anion channelrhodopsin, owing to higher single-channel conductance than that of the known cation conducting ChRs (Wiegert *et al.,* 2017). Recently, Malyshev *et al.,* have shown that GtACR2 can produce both cessation of firing and generation of action potentials in cortical neurons in response to light (Malyshev *et al.,* 2017). This study has opened a very interesting possibility of using the GtACR2 both as cell silencer and cell activator in the same experiment varying the pattern of light stimulation. A more recent screen expanded the family of cryptophyte ACRs to 20 members (Govorunova *et al.,* 2017b). A new ACR, named ZipACR, expressed in cultured mouse hippocampal neuron enabled precise photoinhibition of individual spikes in trains of up to 50 Hz. It is proposed to develop accurate theoretical models of the photoresponse of these inhibitory opsins and verify the experimental. It is proposed to also optimize the conditions of photostimulation of these proteins for better applications.

To determine how precise neural activity patterns mediate computation, behavior and pathology, a set of photoreceptors for reliably activation and inhibition of genetically targeted neurons need to be established. Han & Boyden have experimentally shown that trains of yellow and blue light pulses can drive high-fidelity sequence of hyperpolarizations and depolarizations in neurons simultaneously expressing yellow light-driven halorhodopsin

(NpHR) and blue light-driven ChR2 (Han & Boyden, 2007). To the best of our knowledge there are no theoretical models for simulating this bidirectional control to date. It is proposed to develop an accurate theoretical model to explain the experimental results of bidirectional control of neuronal signaling. To achieve faster and more bidirectional control, the combination of fast excitory protein (Chronos) and inhibitory protein (Jaws/ ZipACR) could be useful (Klapoetke *et al.,* 2014; Chuong *et al.,* 2014; Govorunova *et al.,* 2017b). It is proposed to develop a theoretical model for fast bidirectional control of neuronal signaling, taking these proteins-expressed neurons.

The deep brain stimulation of neurons is one of the urgent requirements for experimental optogenetic studies. In order to optimize the stimulation protocol, two-photon illumination provides better spatial specificity and deep penetration in scattering tissue. Due to high absorption and scattering, visible light, which is the widely used spectrum in optogenetics, cannot reach the inner depth of the brain. Chaigneau *et al.* have demonstrated reliable action potential generation in ReaChR-expressing neurons and studied holographic two-photon evoked spiking performances depending on illumination power and pulse-width (Chaigneau *et al.,* 2015). Recently, two photon holographic photoactivation of Chronos has shown neuronal firing with sub-millisecond optogenetic control (Ronzitti *et al.,* 2016). However the computational modeling of two photon excitation remains to be studied. Hence, It is proposed to develop accurate two-photon stimulation model for the photoresponse of ReaChR/ Chronos to explain the experimental results. It is also proposed to derive optimized conditions for low-power and fast neuronal signaling.

The specific objectives of the proposed thesis are as follows:

1. It is proposed to develop accurate theoretical models for the photoresponse of newly discovered excitory (ReaChR) and inhibitory (Jaws, ZipACR) light-sensitive proteins based on experiments reported recently (Lin *et al.,* 2013; Chuong *et al.,* 2014; Govorunova *et al.,* 2017b).
2. It is proposed to optimize the response in terms of light intensity, wavelength, frequency, pulse-width etc., for better control over neuronal signaling.
3. It is proposed to develop an accurate theoretical model for fast bi-directional control of neuronal signaling using fast excitory (Chronos) and inhibitory proteins (Jaws/ZipACR).
4. It is proposed to formulate an accurate computational model of two-photon illumination of ReaChR/Chronos expressed neurons.
5. It is also proposed to use the optimized neuronal response to design light-controlled neuromorphic computing devices.

## 4. METHODOLOGY

The following steps will be followed to achieve the above objectives:

1. In the first step, the computational studies of ChR2, ChETA and NpHR will be undertaken and the reported results will be reproduced (Nikolic *et al.,* 2009; Grossman *et al.,* 2011, 2013; Stefanescu *et al.,* 2013; Boyle *et al.,* 2015).
2. The experimentally reported photo-kinetics of, ReaChR, Jaws, ZipACR will be analyzed and accurate theoretical models of their respective photoresponse will be formulated (Lin *et al.,* 2013; Chuong *et al.,* 2014; Govorunova *et al.,* 2017).
3. These kinetic models will then be integrated with accurate neuron models (Hodgkin-Huxley model, Wang-Buzaski model, etc.) to verify the results of neuronal spike generation or inhibition, reported in recent path-breaking experimental studies (Lin *et al.,* 2013; Chuong *et al.,* 2014; Govorunova *et al.,* 2017b). Consequently we will optimize the conditions for photostimulation such as light intensity, pulse-width, wavelength, frequency, etc to get optimum control over neuronal signaling.
4. Study of the bi-directional control of neuronal signaling by Han and Boyden, (2007) will then be undertaken, and compared with reported experimental results.
5. An accurate two-photon stimulation model for Chronos and Jaws/ZipACR, will be formulated and the conditions for fast bidirectional control over neuronal signaling will be optimized in terms of intensity, wavelength, frequency, pulse-width etc.
6. By using this optimized control over neuronal signaling, an effort would be made to design neuromorphic switching devices for signal processing.

## 5. Expected Outcomes

The proposed research work will be an important research contribution in the important area of optogenetics. It will lead to accurate models of recently reported experimental results of optogenetic control of neuronal signaling with newly discovered photo-sensitive proteins. It will result in a deeper understanding of not only the photoresponse of these proteins, but also their effect on neuronal signaling.

The proposed research encompasses activation, inhibition and bi-directional control of neuronal signaling and its optimization by optimal values of various physical parameters such as intensity, pulse-width, wavelength, frequency, etc. It would also lead to novel designs of optogenetic based neuromorphic computing devices that have not been reported as yet.

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